Rule-Based Kinetic Modeling of Signal Transduction Networks

Part III. Modeling of EGFR

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http://bionetgen.lanl.gov
Example 1: Early events in signaling by Epidermal Growth factor Receptor
Large networks of proteins and other molecules are involved in signaling

Phenomenological vs. Mechanistic Modeling

- Type of model depends on the questions one wants to ask (and answer).
- *Phenomenological models* are good for establishing correlations among the measured variables.
- *Mechanistic models* attempt to put known information into a model that can describe data and make predictions about how manipulating the components affects the outcome.
Multiplicity of sites and binding partners gives rise to combinatorial complexity

Epidermal growth factor receptor (EGFR)

9 sites $\Rightarrow 2^9 = 512$ phosphorylation states

Each site has $\geq 1$ binding partner
$\Rightarrow$ more than $3^9 = 19,683$ total states

EGFR must form *dimers* to become active
$\Rightarrow$ more than $1.9 \times 10^8$ states
Multiplicity of sites and binding partners gives rise to combinatorial complexity

...but the number of interactions is relatively small.
Early events in EGFR signaling

EGF = epidermal growth factor
EGFR = epidermal growth factor receptor

1. EGF binds EGFR
Early events in EGFR signaling

1. EGF binds EGFR
2. EGFR dimerizes
Early events in EGFR signaling

1. EGF binds EGFR
2. EGFR dimerizes
3. EGFR transphosphorylates itself
Early events in EGFR signaling

Grb2 pathway

1. EGF binds EGFR
2. EGFR dimerizes
3. EGFR transphosphorylates itself
4. Grb2 binds phospho-EGFR
Early events in EGFR signaling

Grb2 pathway

1. EGF binds EGFR
2. EGFR dimerizes
3. EGFR transphosphorylates itself
4. Grb2 binds phospho-EGFR
5. Sos binds Grb2 (Activation Path 1)
Early events in EGFR signaling

Shc pathway

1. EGF binds EGFR
2. EGFR dimerizes
3. EGFR transphosphorylates itself
4. Shc binds phospho-EGFR
Early events in EGFR signaling

Shc pathway

1. EGF binds EGFR
2. EGFR dimerizes
3. EGFR transphosphorylates itself
4. Shc binds phospho-EGFR
5. **EGFR transphosphorylates Shc**
Early events in EGFR signaling

Shc pathway

1. EGF binds EGFR
2. EGFR dimerizes
3. EGFR transphosphorylates itself
4. Shc binds phospho-EGFR
5. EGFR transphosphorylates Shc
6. Grb2 binds phospho-Shc
Early events in EGFR signaling

**Shc pathway**

1. EGF binds EGFR
2. EGFR dimerizes
3. EGFR transphosphorylates itself
4. Shc binds phospho-EGFR
5. EGFR transphosphorylates Shc
6. Grb2 binds phospho-Shc
7. **Sos binds Grb2 (Activation Path 2)**
A conventional model for EGFR signaling

Species: One for every possible modification state of every complex

Reactions: One for every transition among species

Excluded from the scheme

No modified monomers

1. Phosphorylation inhibits dimer breakup

No complexes

2. Adaptor binding is competitive
Summary of the conventional approach

- Combinatorial complexity gives rise to a multitude of species and reactions.
- Modelers assume (often implicitly) only some of these combinations are important.
- Assumptions are based on convenience rather than physical knowledge.
- Assumptions may be valid under some conditions, but not others.
- These assumptions cannot be tested without addressing combinatorial complexity.
Rule-based modeling is a way to handle combinatorial complexity

- **Assumption of proteins modularity:**
  - Signalling molecules consist of functional domains
  - Interactions depend on a limited set of features of signalling molecules, and are “local” with respect to these functional domains.

- The evolution of biological system is defined by **rules** describing activities, potential modifications and interactions of the domains of signaling molecules.

- Computer algorithm **automatically generates** all molecular species and reactions implied by rules.
Instead of the list of species a user specifies

a) Biomolecules and their components

Components of proteins may have attributes, e.g. conformation or phosphorylation state.

b) Species existing before simulation
Instead of the list of reactions a user specifies

c) Rules that generate reactions and species

- User specifies a rule for each **experimentally-testable** feature of the system (Example: *kinetics of ligand-receptor binding is independent of receptor cytosolic tail modifications*).

EGF binds EGFR

Components Y1092 and Y1172 are not shown
Rules generate reactions and new chemical species

Initial set of species

Rule application: reactions

New set of species

All reactions inherit the same rate law.
Extendibility and refinement of rules

Revise rules to account for context (steric clashes, cooperativity).
Predictions are reported as “observables”, corresponding to groups of species with the same properties.

Pattern that selects EGFR phosphorylated at Y1092.
BioNetGen modeling

Input: components, rules of interactions

Model: species and reactions

Solution: timecourses of all species

Simultaneous network generation and time courses computations

Sequential network generation and time courses computations

ODE's

SSA

Observables

Specific complexes
Rule-based version of a reaction scheme

18 species
34 reactions
37 parameters

356 species
3749 reactions


- Same number of parameters as in reaction scheme
- Physical basis for rate parameters (e.g. binding constants)

Rule-based version of the Kholodenko model

- 5 molecule types
- 23 reaction rules
- No new rate parameters (!)

18 species
34 reactions

356 species
3749 reactions

BioNetGen and BioNetGen Language (BNGL)
Representation of biomolecules

Nodes represent components of proteins

Components may have attributes: 〇 or 〇
Representation of complexes

An EGFR dimer

Edges represent bonds between components

Bonds may be internal or external
Patterns select sets of chemical species with common features

*Pattern that selects EGFR phosphorylated at Y1092.*
Patterns select sets of chemical species with common features

*Pattern that selects EGFR phosphorylated at Y1092.*

EGFR suppressed components don’t affect match

inverse indicates any bonding state

selects twice
Reaction rules, composed of patterns, generalize reactions

EGF binds EGFR

unfilled components must be unbound

Patterns select reactants and specify graph transformation
- Addition of bond between EGF and EGFR
Reaction rules, composed of patterns, generalize reactions

EGF binds EGFR

Each rule may generate many reactions and species
Reaction rules, composed of patterns, generalize reactions

EGF binds EGFR

\[ \text{EGF} + \text{EGFR} \xrightarrow{k_{+1}} \text{I-III} \xrightarrow{k_{-1}} \text{II} \]

All reactions inherit the same rate law. Assumes that only features represented in the rule affect the rate of reaction.
EGF binds EGFR

**Reactant patterns**

\[ \text{EGF}(b) + \text{R}(L,d) \leftrightarrow \text{EGF}(b!1).\text{R}(l!1,d) \]

**Product pattern**

**Rate law(s)**

\[ k_{+1}, k_{-1} \]

- **molecule**
- **components (unbound)**
- **a bond**
Observables define model outputs

EGFR(Y1092~P!?)

EGFR phosphorylated at Y1092

EGFR(Y1172~P!1).Shc(PTB!1)

Shc associated with pEGFR
Elements of the BNGL file

Input to BNG is written in a file with the .bngl extension.

begin parameters
dend parameters

begin molecule types
dend molecule types

begin seed species
dend seed species

begin reaction rules
dend reaction rules

begin observables
dend observables

command1
command2
...

Parameters

begin parameters
  Na  6.0e23
  V   1e-12
  kpl 3e6/(Na*V)
  km1 1.0
end parameters
molecule types

\[
\text{begin molecule types} \\
\quad A(b) \quad \rightarrow \quad \text{O} \\
\quad B(a) \quad \rightarrow \quad \text{O} \\
\text{end molecule types}
\]
seed species

begin seed species
  A(b) 1000
  B(a) 500
end seed species
reaction rules

\[ A(b) + B(a) \leftrightarrow A(b!1).B(a!1) \text{ kp1, km1} \]

end reaction rules
simulation commands

generate_network({overwrite=>1});
simulate_ode({t_end=>>20,n_steps=>>20});

/Users/faeder/shared/Projects/BioNetGen_develop/Perl2/BNG2.pl
BioNetGen version 2.0.40+
Reading from file simple.bngl
Read 4 parameters.
Read 2 molecule types.
Read 2 species.
Read 1 reaction rule(s).
WARNING: Removing old network file simple.net.
Iteration 0: 2 species 0 rxns 0.00e+00 CPU s
Iteration 1: 3 species 1 rxns 1.00e-02 CPU s
Iteration 2: 3 species 2 rxns 0.00e+00 CPU s
Grand challenge: create a comprehensive rule-based model